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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/783,320	02/15/2001	D. Wade Walke	LEX-0137-USA	3185

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EXAMINER
RAMIREZ, DELIA M

ART UNIT	PAPER NUMBER
1652	18

DATE MAILED: 05/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/783,320	WALKE ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 25 April 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *18 March 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attached*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *none*.

   Claim(s) objected to: *none*.

   Claim(s) rejected: *4,11 and 12*.

   Claim(s) withdrawn from consideration: *5,13 and 14*.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☒ Other: *PTO-892*

ADVISORY ACTION

1. Claims 4-5, 11-14 are pending.

2. As indicated in previous Office Action Paper No. 14, mailed 12/1/7/2002, this application contains claims 5, 13, and 14 drawn to an invention nonelected with traverse in Paper No. 10.

3. The request for reconsideration filed on 4/25/2003 under 37 CFR 1.116 in reply to the Final Action Paper No. 14 mailed on 12/1/7/2002 has been considered but is not deemed to place the application in condition for allowance for the following reasons.

4. Applicants argue that the Examiner fails to recognize Applicant's assertion that the present invention is a human kinase, in particular a human NEK-1. Applicants argue that this is clearly credible and supported by the evidence provided in Exhibits C-E submitted by Applicants in Paper No. 13. Applicants submit that the Examiner may not be familiar with the International Protein Index, which is a publicly available database. To clarify Applicant's assertion, Applicants submit an alignment of SEQ ID NO: 4 and accession number IPI00044749.2 in Exhibit A and an alignment of SEQ ID NO: 4 and Swiss Prot accession number Q96PY6 in Exhibit B. According to Applicants, the results of both comparisons clearly show identity between the sequences of the present invention and a human serine/threonine kinase NEK-1. Applicants assert that the present invention encodes a human kinase which is a shorter form of NEK-1. Applicants further argue that Bork (Genome Research, 10:398-400, 2000) does not refute the value of sequence analysis and that Bork teaches that there is room for improvement. In regard to Broun et al. (Science 282:1315-1317, 1998) and Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995), Applicants argue that there is only one example in which function

annotation based on sequence homology was incorrect. Therefore, it is Applicant's opinion that one example is not indicative of a high level of uncertainty and does not support the alleged lack of utility.

Applicants further assert that the claimed polynucleotides can be used in gene chip applications and that there is no need to know the exact function or role of the claimed invention to track expression patterns using a DNA chip. According to Applicants, the claimed polynucleotides provide specific markers of the human genome and that such specific markers are targets for discovering drugs that are associated with human disease. Therefore, Applicants submit that the instant polynucleotides are an ideal candidate for assessing gene expression using DNA chips and that those DNA chips, i.e. those comprising the claimed polynucleotides, would have utility as evidenced by hundreds of issued patents regarding DNA chips.

Applicants submit that only a small percentage of the genome encodes exons, therefore not all genomic DNA can be used in such chip applications. As such, use of the claimed polynucleotides in a DNA chip is not generic. Applicants further argue that evidence of the "real world" substantial utility of the present invention is provided by the fact that there is an entire industry worth millions of dollars established based on the use of gene sequences or fragments thereof in a gene chip format and that billions of dollars have been invested in the human genome project, therefore demonstrating the usefulness of human genomic data such as that of the present invention. Applicants contend that the claimed polynucleotides have substantial and credible utility based on the billions of dollars invested and the numerous companies focused on such information and well-established utility since the utility of human genome data has been understood for many years.

According to Applicants, the claimed polynucleotides have specific utility since they can be used to determine the genomic structure of the corresponding human chromosome. It is Applicant's contention that the claimed polynucleotides provide exquisite specificity in localizing the specific region of the chromosome containing the gene encoding the given polynucleotide. Applicants further submit that the present polynucleotides provide biologically validated empirical data that specifically define that portion of the corresponding genomic locus that actually encodes an exon. Applicants submit a BLAST analysis which compares SEQ ID NO: 3 to identified human genomic sequence and indicate that the polynucleotide of the instant invention comprises 31 exons spread non-contiguously along a region of human chromosome 4. Furthermore, Applicants argue that their polynucleotide maps to the same region of human chromosome 4 (4q32.3) therefore supporting Applicant's position that the claimed polynucleotides encode a variant of the human NEK-1 kinase.

Applicants submit that it is improper for the Examiner to hold Applicant's invention to a different legal standard of patentability. Applicants argue that it is unclear as to how an invention fully disclosed and free of the prior art can retain less utility and be less enabled than inventions already patented which were filed when the level of skill in the art was clearly lower. In regard to the rejection of claims 4, 11 and 12 under 35 USC, 112 first paragraph, Applicants submit that since the claimed invention has a specific, substantial and credible utility, this rejection should be withdrawn.

5. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the utility rejection. In regard to Exhibits A and B, it is noted that accession number IPI00044749.2 and previously submitted Swiss Prot accession number Q96PY6 are the same

entry. This is easily determined by comparison of both alignments provided which show (1) the number of amino acids in both entries (IPI00044749.2 and Q96PY6) is the same (1258 aa), (2) the regions of identity are the same, (3) the regions of non-identity are the same, and (4) the Smith -Waterman score in both alignments is identical, i.e. 96.343%. As indicated previously, while one could argue that the polynucleotide of Nagase et al. (Q96PY6) is highly homologous to the claimed polynucleotide, the annotated function for the polynucleotide of Nagase et al. is a putative function, based solely on structural homology and not empirically determined. As such, there is no empirically validated data to support Applicant's assertion that the claimed polynucleotide is a short variant of a human NEK-1 protein.

In regard to the references presented by the Examiner, it is noted that the Examiner does not contend that there is no value in sequence analysis however as admitted by Applicants, accurate functional annotation needs improvement. While in some cases, predictions of function based on sequence homology may have been proven accurate, the state of the art as discussed previously indicates that 67% structural homologs, as taught by Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) or even 98% structural homologs, as taught by Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) were not functional homologs. In addition, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Therefore, in view of the evidence presented in regard to Broun et al., Van de Loo et al., Seffernick et al. and Witkowski et al., one of skill in the art would require some knowledge or guidance as to which are the critical structural elements

required to have the desired function since, the state of the art teaches the unpredictability of accurately assigning function based solely on structural homology.

In regard to use of the claimed polynucleotides in DNA chips, it is noted that the specification is silent in regard to how expression of the claimed polynucleotides correlates with disease. As such it is unclear as to how one can reasonably conclude that the claimed polynucleotides can be specific markers of the human genome or how one could interpret expression patterns in a DNA chip.

The Examiner acknowledges that (1) only a small percentage of the genome comprises exons, (2) there is an entire industry worth millions of dollars established based on the use of DNA chips, (3) billions of dollars have been invested in the human genome project, and (4) human genomic data is useful, however the Examiner disagrees with Applicant's contention that the claimed polynucleotides have "real world" substantial utility. As indicated above, in the absence of information as to how expression of the claimed polynucleotide correlates with a disease, it is unclear as to how one of skill in the art can interpret expression patters using a DNA chip. One of skill in the art would require further research to corroborate Applicant's asserted function in addition to determine which are the biological processes and/or conditions which are associated with the expression of the claimed polynucleotides before one can use DNA chips which would allow the discovery of drugs.

In regard to arguments that the claimed polynucleotides have specific utility since they can be used to determine the genomic structure of the corresponding human chromosome, it is noted that any polynucleotide in human chromosome 4 can be used to identify that chromosome. Also, it is noted that while Applicants assert that the claimed polynucleotide comprises 31 exons,

no empirical determination has been made to corroborate that the claimed polynucleotide contains 31exons. Therefore, it is unclear to the Examiner as to how the information provided by Applicants is validated empirical data or if one can use the claimed polynucleotide to map coding exons. It is also noted that in view of the fact that there is no empirical corroboration that 4q.32.3 corresponds to a gene encoding a human NEK-1 kinase, one cannot reasonably conclude that the claimed polynucleotide encodes a human NEK-1 kinase.

6. In regard to arguments that the Examiner is holding Applicants to a different legal standard of patentability and that other inventions which have been patented are less enabled and have less utility than Applicant's, it is noted that each application is examined on its own merits and that the Examiner must examine a patent application according to the guidelines set forth by the USPTO as well as the MPEP, since the Examiner has no authority to disregard such guidelines or to apply her own interpretation of patent law in the examination of the application. In the instant case, the Examiner has used the current Utility Guidelines as set forth by the USPTO. It is also noted that any discussion in regard to the utility and enablement of other inventions would be improper herein since it will require a detailed review of the record in each case. Since claims 4, 11 and 12 are deemed unpatentable in view of lack of utility as set forth above, the 35 USC 112, first paragraph rejection is maintained for the reasons of record.

7. For purposes of Appeal, the status of the claims is as follows:

Claim(s) allowed: NONE

Claims(s) objected to: NONE

Claim(s) rejected: 4, 11 and 12

Claim(s) withdrawn from consideration: 5, 13 and 14

8. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

9. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
May 9, 2003

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP 1~~800~~
1600